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HAIR

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The psychologic importance of hair to man is in inverse ratio to its physical function. Except for scalp hair and desultory areas of sexual hair, most of man's hair follicles are vestigial. Three problems of hair growth remain to be solved: (1) how the intermittent activity of hair follicles in both animals and man is controlled; (2) how the male hormone alters the hair cycle in human skin; and (3) why larger hairs are produced by testosterone in some areas of the body when in some individuals the hair follicles in the scalp regress.

Studies in which skin grafts from rats of different ages were exchanged showed that hair follicles are innately programmed but can be slowly influenced by systemic factors. Steroid hormones, especially estrogens, slow down the moult cycle whereas thryoid hormones accelerate it. What establishes the innate rhythm remains problematical. The fact that plucking out the club hair initiates activity in resting follicles has been explained by the hypothesis that the mitotic inhibitor which accumulates during anagen is normally used up or dispersed during telogen or by wounding. However, contrary to this theory, follicular activity is not prolonged by epilation during anagen. Moreover, if rats are epilated within one or two days of eruption, only club hairs are removed since forceps cannot grasp the tips of the new hairs. Such epilation does not affect the anagen in progress, but remarkably enough the subsequent resting phase is shortened.

Both sexual hair and male-pattern baldness depend on androgenic hormones. Target organs of testosterone convert the hormone to active metabolites, chiefly 5α-dihydrotestosterone. In skin, however, 5α-dihydrotestosterone may not be the only active tissue androgen. The major metabolite of testosterone incubated with hair roots is androstenedione, and hirsute women without other obvious endocrine abnormality sometimes excrete high levels of androstanediol. Both steroids stimulated the sebaceous glands of hypophysectomized–castrated rats, which, however, showed only a limited response to testosterone. The androgenic steroids, the enzymes that convert them to their active metabolites, and the proteins that bind them are undoubtedly very important to the problems of the growth of sexual hair and of male-pattern baldness.

Hair performs no vital function whatsoever in man whose body could be perpetually depilated or shaved without any physiologic disadvantages. But, the psychologic functions of hair seem almost immeasurable. Scalp hair is a major social and sexual display feature of the human body: for women, the crowning glory of decently exposable femininity; for men, a traditional symbol of masculinity. If the lack of scalp hair is a disaster for women, excessive facial or body hair beyond the cultural norm set by the society in which they live can be almost as distressing. It is little comfort to such a woman to be told she has idiopathic hirsutism! Hair cannot, therefore, be scientifically ignored. But how are the complex and seemingly insuperable problems of hair growth to be solved? Is it possible to make any useful hypotheses about human hair follicles from experiments carried out on animal models?

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The evolutionary history of hair is so confused as to utterly mislead the comparative zoologist, let alone the biochemist with perhaps a less subtle appreciation of natural selection. How often, for example, do we read of some material being tested on hair growth in the guinea pig as if the experiment were somehow related to the alleviation of human-pattern alopecia? The difficulty arises from the versatile function of the hair follicle. We do not know how or where hairs originated in evolution or what was their original purpose. Perhaps, as Maderson [1] and others have suggested, they first arose as part of mechanoreceptor units, developing in the hinge regions between the scales of some reptilian ancestor. Certainly, the evolutionary success of the warm-blooded mammals owes much, if not all, to the properties of a hairy pelage as a heat insulator. To judge by the popularity of fur coats and wool garments, the fiber produced by the hair follicle still holds its own against the artifacts of modern technology.

These considerations do nothing to explain any

selective advantages of hair to man. Human hair follicles are still sense organs and to tug the hair causes pain, but men do not explore their environments with vibrissae. And if the survival of the hairy mammals is due to their ability to keep warm, the emergence of global man depended on his capacity to keep cool. The highly vascular human skin, which can switch from radiating heat to conserving it by shunting the blood flow below a layer of insulating fat and, conversely, can increase heat loss by evaporating sweat from millions of glands, is a far more adaptable structure than the slowly moulting animal pelage.

Most of our hair follicles are vestigial. At best, our hairy heritage is now represented by scalp hair, perhaps as a protection against the noonday tropical sun before the invention of hats, and by desultory areas of so-called sexual hair. These are clearly of two types. The male beard must be compared to the lion's mane and other similar structures; it is a secondary sexual character, whatever that may mean. Presumably it was originally more concerned with aggressive displays against other males than with sex appeal to females, which may explain why many of us shave it off in our supposedly nonaggressive, peaceful, and cooperative societies. The remainder of the sexual hair, the pubic and axillary, common to males and females alike, is, I believe, more likely to be concerned with disseminating glandular odor than (as some authors have suggested) with preventing friction burns in weight lifting, sexual intercourse, and other heavy exercise.

Chase and Eaton [2,3] and Argyris [4–6] were among those who pioneered the experimental study of the control of the hair follicle, the one stressing the role of inhibitors, the other that of wound hormones. Van Scott and co-workers were responsible for magnificent balsa wood reconstructions of pilosebaceous apparatus [7] as well as for important studies of alopecia areata [8,9]. Pinkus [10] wrote an authoritative account of the embryology of the hair follicle, drawing largely from the original observations of his illustrious father. Kligman [11] provided a classic account of the human hair cycle which included the first description of catagen in scalp follicles as well as one of the first descriptions of human hair loss in terms of the dynamics of the follicle [12]. Hair growth was and has remained one of the foremost interests of William Montagna, an interest with which he has successfully infected a long line of colleagues and pupils.

I shall describe my own data concerning hair growth and shall leave anatomy, embryology, histology, histochemistry, and electron micrography strictly alone. I must omit the interesting and important experimental studies of Cohen [13] and Oliver [14,15] on the interactions between the dermal papilla and the epidermis in the induction of hair follicles. For me, there are two major problems to consider. What controls the cyclic activity of the hair follicle? How does male hormone alter the cycle in the human skin and, in particular, why does it produce larger hairs in some areas of the body but, in some individuals, cause the follicles in the scalp to regress?

THE CONTROL OF THE HAIR CYCLE

That virtually all hair follicles undergo cycles of activity in which an active phase (anagen) alternates with a resting phase (telogen) is known to all. Such cycles occur not only in species which show well-marked patterns of moult as the animals grow up or as the seasons change, but also in species, such as the guinea pig, which do not. Probably there is no sharp distinction between the forms. Follicular activity in guinea pigs is not synchronized within each region to the same extent as it is in rats or mice, but neither does it, at least in young animals, occur at random. Pulse labeling with [^{35}S]cysteine reveals that activity is to some extent synchronized within each of several different follicle types which are, however, out of phase with each other [16]. The follicles in the neonatal human scalp appear to show a measure of synchrony [17], as do the follicles within each trio group throughout the body [18].

What controls the cyclic activity of hair follicles? Experiments on laboratory rats, in which the moults are not only very well marked in adolescence but continue throughout life even under constant environmental conditions, have thrown some light on the problem. Before each moult, follicle activity starts in the ventral region and moves dorsally across the flanks; production of the new hairs is followed by shedding of the clubs formed in the previous cycle. There are various ways, as we shall see, in which the passage of the moult can be accelerated or delayed, but it always occurs in sequence (for reviews, see [19,20]).

Leaving aside the problem of what triggers the start of the moult, the hypothesis that it spreads by propagation, that each active follicle somehow stimulates its immediate neighbor, is as attractive as it is erroneous. The experimental evidence against it is clear-cut. When a full-thickness skin autograft about 15 mm wide is made in the flank of a rat while the follicles are in telogen, the advancing front of the next wave of activity on the graft remains behind that on the adjacent flank [21]. If the wave of activity were propagated, one would expect that follicles dorsal to the graft would not become active until the front advancing over the graft had reached the dorsal margin. In fact, they become active synchronously with those on the adjacent ungrafted flank.

If hair follicles are independent of each other, is each follicle then inherently programmed, or does each follicle individually respond to a common systemic stimulus? When the position of follicles is altered by rotating or transposing grafts, the follicles largely continue in the rhythms of their original sites, although a small site effect can be demonstrated. However, this experimental evidence does not resolve the issue since it can be

argued that follicles do not necessarily have an innate program, only a site-characteristic response to some systemic factor. The problem can be solved only by exchanging homografts between rats of different ages in different stages of the moult cycle. It is necessary to compare each homograft with autografts made on the opposite flanks of the donor and recipient, respectively. Such experiments (Fig. 1) show that the homografts at first continue in the same rhythm as the donor autografts, but that gradually over many weeks they come into phase with autografts on the recipients [22]. So do the hair cycles of parabiotically joined rats of unequal age [23]. It appears, therefore, that follicles are innately programmed, but that they can also be slowly influenced by systemic factors. The finding is perhaps not surprising since moulting is influenced by external changes in environment, of which the photoperiod seems to be the most important, though temperature may exert a small modifying influence (see [20]).

While a definitive statement of the systemic factors responsible for mediating between environment and follicle cannot be given, several hormonal systems profoundly affect the moult cycle. Steroid hormones, especially estrogens, act as a brake, whereas thyroid hormones accelerate. For example, in intact female rats, generation 3 (i.e., the second postnatal replacement of hair) of follicular activity starts in the ventral region at about 63 days of age, reaches the dorsum by 90 days, and is complete by a little after 150 days. In the spayed animal, the wave reaches the dorsum by 66 days and is complete at about 92 days, that is, about 60 days earlier than in the intact. If estradiol is implanted, the wave does not reach the dorsum by 110 days [24,25].

In contrast, thyroxine greatly accelerates the

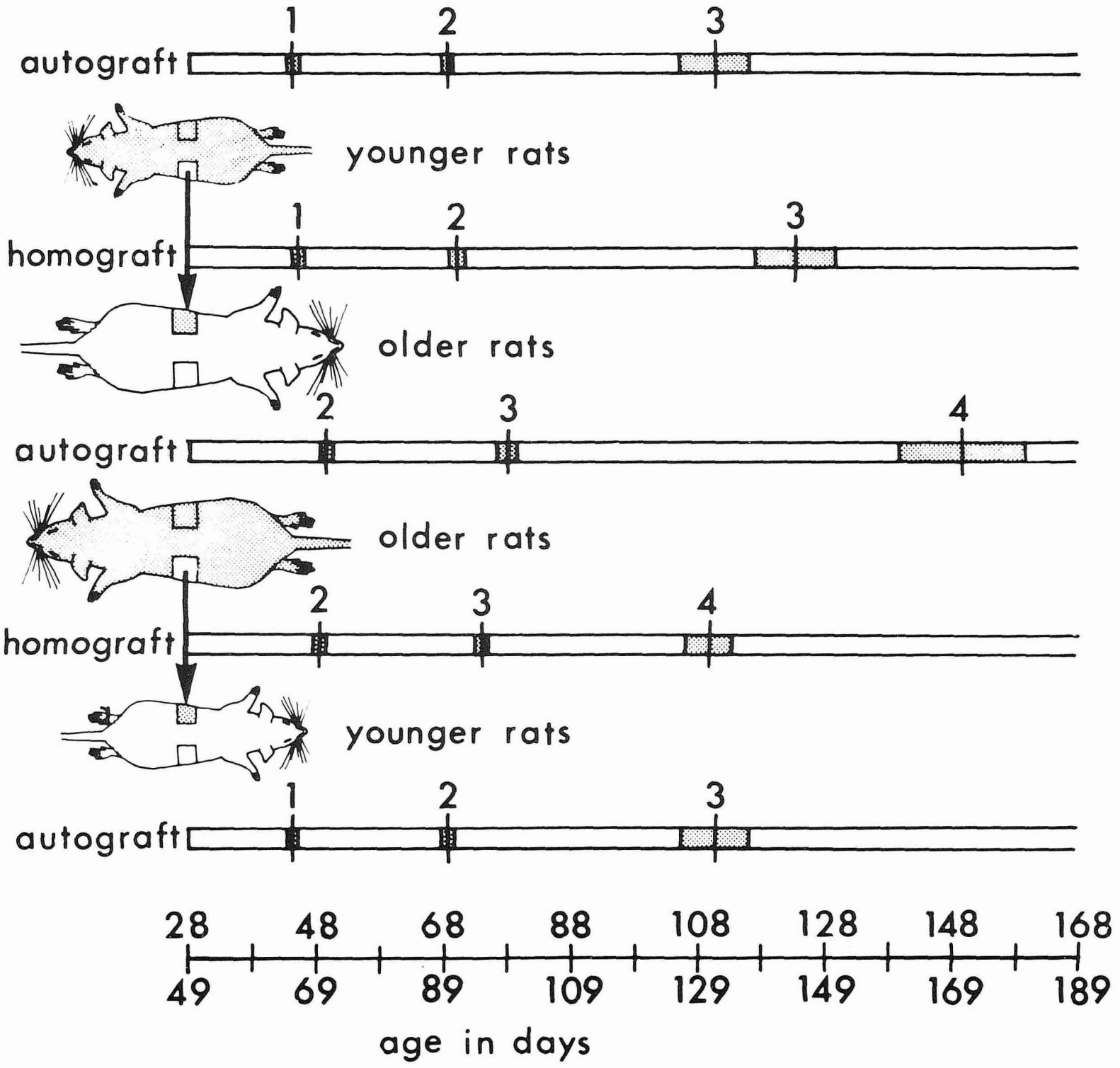

FIG. 1. Successive eruptions of hair on homografts exchanged between rats aged 28 and 49 days, respectively, and on autografts made at the same time. *Shade limits* represent plus or minus 1.5 times the standard errors for a minimum of 9 observations of the sequential eruptions.

passage of the moult. Thus, intact female rats given 100 μg of thyroxine per day completed the moult in 96 days, at about the same age as untreated spayed rats. On the other hand, treatment with propylthiouracil greatly delayed the moult so that the mid-dorsum was not reached until after 170 days and the moult had not been completed at 260 days [19,26].

The daily rate of elongation and the definitive length of the hairs are significantly affected by hormones, i.e., they are reduced by estrogens and increased by thyroxine. After pulse-labeling with [^{35}S]cysteine, the duration of anagen in each particular region can be reduced by thyroxine and, perhaps paradoxically, also by estrogen [27]. But these effects are slight compared with those on the duration of telogen. Hormones apparently exercise considerable control over quiescent follicles, but once anagen starts, the hormonal effect becomes relatively slight.

We must conclude, therefore, that the hair follicle is controlled by both local and systemic factors. Each follicle has an intrinsic cycle characteristic of its region, but especially in respect to the initiation of anagen and to a limited extent during activity, it is at the same time susceptible to hormonal systemic influences.

But what controls the intrinsic cycle? Chase [2] and Chase and Eaton [3] pioneered the hypothesis that a mitotic inhibitor accumulates during anagen and is gradually used up or dispersed during telogen. This has much in common with Bullough's theory that cell division is normally held in check by tissue-specific chalones [28]. The best evidence of the inhibitor hypothesis is that anagen can be initiated by plucking the club hair from a resting follicle or by wounding, the inference being that an accumulated inhibitor is removed or dispersed. It might then be imagined that systemic hormones could act by modifying the dermal environment to influence the rate of dispersal of the inhibitor. In fact, there are profound changes in the dermis during the follicular cycle, including regular fluctuations in collagen and fat [29] as well as mast cells, histamine, and serotonin [30]. However, under hormonal treatments, the changes in the hair follicle and in the dermis remain strictly in phase, so it is, in my view, impossible to claim that either one is the cause of the other.

Follicular activity, revealed by the uptake of tritiated thymidine, starts about 10 hr after epilation [31]. The external eruption of hairs, i.e., the emergence of monotrichs and awls (about 1 to 2 days earlier than auchenes and zigzags) occurs in the dorsal flank of intact rats about 11 days after plucking [27] and on the midflank a little sooner (Fig. 2). Keratinization commences at the tips of the new hairs 6 to 8 days before eruption. The response of the follicle to plucking is slightly but significantly affected by hormones, the interval being shortened by spaying or thyroxine and lengthened by estrogen or propylthiouracil. A meticulous study by pulse labeling with [^{35}S]cysteine

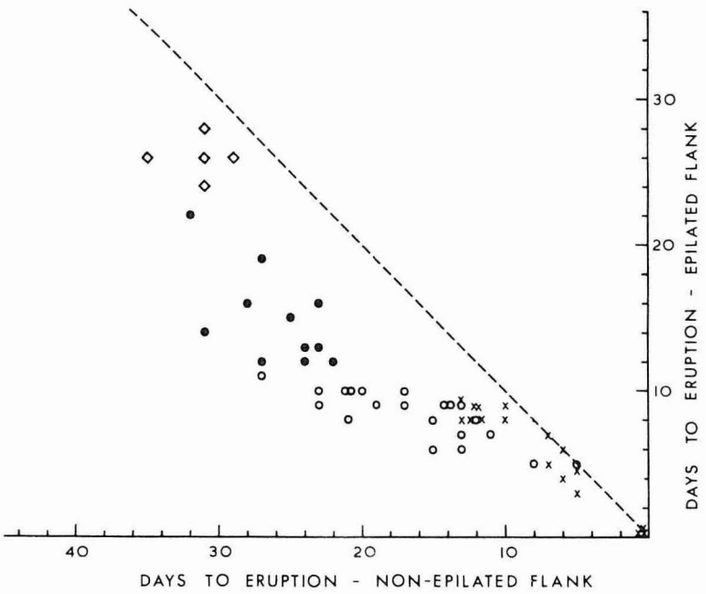

FIG. 2. The effect of epilation of follicles in the midflank of intact female rats on the next eruption. The number of days to eruption on the epilated flank is plotted against the time to eruption on the control nonepilated flank. Plucking of club hairs more than 10 days before expected eruption induces eruption after 8 to 10 days. Plucking of club hairs less than 10 days before expected eruption, when follicles are already active, has little or no effect on the time of eruption. Plucking growing hairs advances next eruption even more than plucking club hairs. Plucking G1 club hairs from alongside newly erupted G2 hairs does not affect their growth but shortens the ensuing telogen. O, G2 club hairs; ●, G2 growing hairs; Δ, G1 club hairs from alongside recently erupted G2 hairs; ×, G1 club hairs.

reveals that epilation has no effect on the ultimate length, duration of growth, or mean rate of growth of the hairs [27]. This holds for rats under hormonal treatments as well as for normal animals; i.e., hormonal treatments have exactly the same effect on active follicles regardless of whether the activity was spontaneous or induced by epilation. Epilation, which acts solely to break telogen, can be compared to the setting of an alarm clock: the time at which the alarm goes off (or the hairs erupt) is changed without altering the duration of the peel (or the growth of the hairs).

All this reveals nothing of how the active hair follicles enter catagen or, indeed, of why epilation of telogen hairs induces anagen. If the cause of quiescence were the build-up of an inhibitor, one might expect that the follicle could be kept in continuous activity by plucking the growing hairs and thus dispersing the inhibitory substance. But this does not happen; if anything, removing the growing hairs shortens rather than lengthens the duration of anagen [32]. However, such evidence against the inhibitory theory is by no means conclusive since it can, with some factual support, be argued that to wrench out growing hairs causes considerable damage to the follicle [33,34]. Indeed, repeated plucking reduces the number of follicles with normal growing hairs and, according to Hamilton and Potten [35], destroys the stimulus-responsive cells.

Some new experimental evidence relating to this problem can now be offered. If rats are epilated

within 1 or 2 days of eruption, the only removable hairs are clubs, since the tips of the new hairs do not yet protrude far enough to be grasped by forceps. Such epilation has no effect whatsoever on the duration of the anagen in progress [27]. The new hairs continue to elongate, and the follicles to enter catagen after the normal interval, completely ignoring the removal of the old club. A remarkable consequence, however, is that the ensuing telogen phase is shorter than normal, that is to say, the next eruption is advanced. Figure 3 shows the mean advance of successive eruptions after a single epilation carried out at various stages of the cycle. Plucking of club hairs about the time of spontaneous eruption does not affect it (first eruption), but the next eruption (second eruption) is about 6 days earlier.

This evidence cannot easily be reconciled with the view that inhibitor builds up to a maximum towards the end of anagen and disperses during telogen to the point where the follicle again becomes active. On the contrary, in this experimental situation, initiation of activity does not appear to be directly related to the termination of the previous anagen but to a chain of events set in motion by the removal of club hairs when anagen was already under way.

In summary, we know little about the mechanism of the intrinsic cycle except that the facts cannot all be explained by the inhibitor build-up hypothesis. It has, however, been clearly established that during the resting phase the initiation of anagen can be profoundly influenced by systemic factors such as hormones which can advance or retard it by several weeks or by plucking the club which virtually overrides the other controls. Do epilated follicles remain permanently out of phase or, like transplanted follicles on grafts, is the timing of eruption slowly influenced by systemic factors? Evidence suggests that follicles do more than simply remain out of phase (Fig. 3). In the cycle immediately succeeding the induced one, the effect is enhanced and anagen becomes even further advanced.

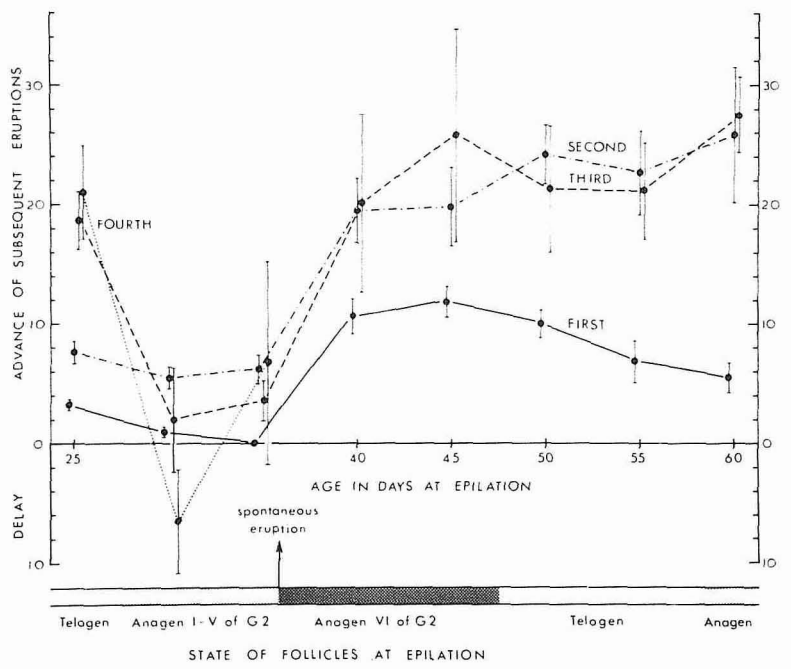

FIG. 3. The advance of successive eruptions of hair after a single epilation in the midflank, shown in relation to the age of the rats and the stage of the cycle at which epilation was carried out. Means ± SEM are for groups of 4 to 6 intact female rats. The first eruption after epilation is advanced, except where club hairs were plucked from follicles already in anagen. The effect was greatest when growing hairs were plucked. The second eruption is even more advanced, by an additional 10 days or more, than the first. The third eruption remains advanced by about the same amount as the second.

The cyclic activity of the hair follicle clearly remains a fascinating problem of experimental biology with the final solution still a glittering prize. But what is the relevance, if any, of these animal experiments to human problems? Do they, for example, shed any light on conditions in which scalp hair becomes thin? Certain types of transient alopecia have been ascribed to alterations in the hair cycle. Postpartum shedding of hair, for example, appears to involve the simultaneous precipitation into catagen of large numbers of follicles, supposedly as a consequence of the withdrawal of circulating hormones which prevented the normal process in late pregnancy when an exceptionally high proportion of follicles are in anagen [36].

A similar kind of hair loss sometimes occurs within 2 to 3 months of febrile episodes such as typhoid fever, scarlet fever, or pneumonia. Kligman [12] proposed that the phenomenon be called "telogen effluvium" and believed that some hair loss of apparently psychogenic origin is of this type. He recounts the case of a prisoner, under his close surveillance, who had been implicated in a murder and had stood trial on three occasions, each time escaping the death penalty on a legal technicality. His uncertain status in this world continued for a period of about 3 years, until in a fourth trial he was convicted of murder in the first degree. About a month later he presented transverse depressions (Beau's lines) in the proximal portions of all his fingernails and became showered with scales from an extraordinary amount of simple dandruff. About 10 weeks after the sentence he started to complain of hair loss, and by fanatically saving every hair, he even managed to convince Kligman that he had shed between 600 and 1500 hairs per days for a period of 3 weeks. Kligman records that telogen counts were about 50%, that substantial restitution started about 8 weeks after shedding, and that when the prisoner was subsequently pardoned his hair regrew completely.

Hair is also rapidly shed in alopecia areata. Lesions usually appear to start a focal point and spread outwards to form patches, but the process can occur diffusely. A study [37] in which hairs were successively plucked in a series of concentric rings from developing lesions showed that at an early stage 100% of the hairs removed from the center of the patch were club hairs and that a wave of telogen appeared to move centripetally. Two other features of alopecia areata are the occurrence of short protruding club hairs with a frayed point, often known as "exclamation marks," and the

appearance as the lesions progress, of many follicles in a state of arrested anagen [8,9,38]. The simplest hypothesis to explain all these facts is that a transitory failure near the matrix causes the anagen hair to shed and that shearing of hair from follicles moving into catagen produces the truncated protruding exclamation mark hairs (Fig. 4). Since the follicles already in telogen remain unaffected, the only remaining hairs that can be plucked are club hairs. However, we cannot be sure that the disorder does not also precipitate follicles into catagen as Eckert et al originally proposed [37]. At least, a knowledge of the hair cycle enables us to understand somewhat the progress of the lesion, even if it provides no clue as to its cause.

The facts about male type baldness, such as they are, are widely known and can be rapidly summarized. The clinical manifestations, namely, the gradual replacement over symmetrically patterned areas of the scalp of good quality terminal hairs by cosmetically useless fluff, has been amply described, not only in man but in even more detail in splendid studies of the stump-tailed macaque [39,40]. Metabolically, the follicles do not appear altered. The only etiologic clue is that, even in subjects with an hereditary disposition to early baldness, the male testicular hormone testosterone is necessary for its manifestation. This single fact overrides all others.

Male type hormones are unquestionably the agents which at puberty cause growth of pubic and axillary hair and transform the vellus follicles of the face into a beard. An indirect demonstration of this fact concerns a young Englishman [41] who had to spend periods of several weeks on a remote island and consequently had no opportunity for sexual activity. He noticed, however, that his beard grew faster (as measured by weighed shavings) on the day before he was to leave the island. Growth reached a maximum during the first days of resumed sexual intercourse but declined to normal within 4 to 6 days. That the effects were due to fluctuations in androgen levels was supported by a clear correlation between beard growth and sebum production. After the results were described in *Nature* [41], a popular organ of the British press reported "Sexual intercourse makes the beard grow." *The Times* of London, ever respectable, reported "Sexual abstinence makes the beard grow." Neither was correct. The true interpretation of the anonymous results is that anticipation makes the beard grow.

The response of target organs to testosterone is dependent upon its conversion to metabolites, of which 5α-dihydrotestosterone is the most important (for review, see [42]). 5α-Reduction of testosterone was first established for the prostate, but it appears to be equally necessary for the responses of other organs, including the seminal vesicles, preputial glands, and skin [43]. The limitation of sexual hair to certain areas is almost certainly related to the local capacity of the skin to carry out this conversion. For example, the scrotal skin of

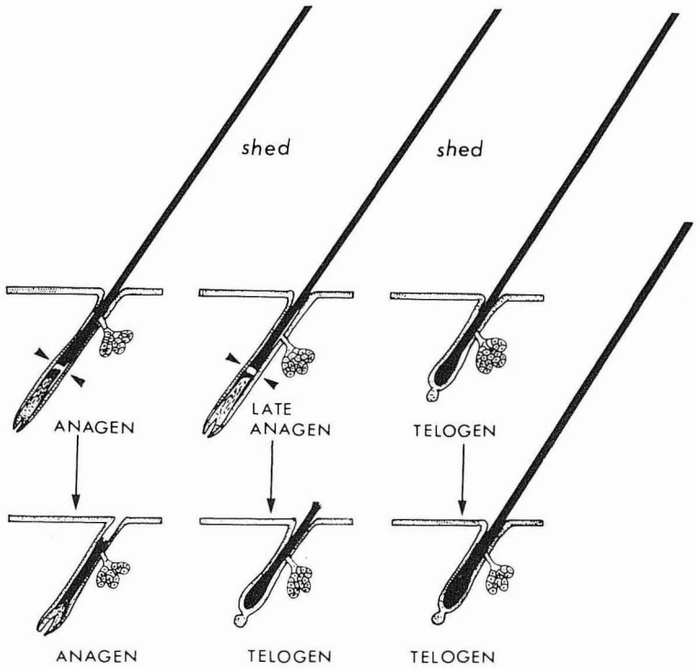

FIG. 4. Simplest explanation of phenomena observed in development of lesions in alopecia areata.

adult human males has a very much greater ability than abdominal skin to convert testosterone [4-^{14}C] to 5α-dihydrotestosterone [44]. What is perhaps even more interesting is that fetal skin from the genital areas has the same ability.

Why, then, does testosterone, which on the face and some other regions of the body causes follicles to switch their hair production from vellus to terminal, apparently have the opposite effect in the scalp?

Adachi et al [45] attempted to formulate a hypothesis to explain the development of pattern alopecia. From plucked growing scalp hairs, they extracted adenyl cyclase, the enzyme responsible for producing cyclic AMP, which is accepted as a common mediator of hormonal action at the cellular level and is normally increased by hormonal stimulation. They showed that adenyl cyclase could be inhibited in vitro by 5α-dihydrotestosterone, but not by testosterone. They suggested that such a decrease would limit the energy metabolism and protein synthesis in hair follicles in vivo.

Leaving aside the question of why 5α-dihydrotestosterone should inhibit rather than enhance adenyl cyclase in the scalp, it is clear that this hypothesis requires that bald skin should convert testosterone more readily than hairy skin. The evidence of Bingham and Shaw [46,47] suggests that this may be true, even if it does not firmly establish it. They incubated male scalp skin from bald and hairy sites with [4-^{14}C]testosterone. In each of four donors, both the uptake and metabolism of testosterone were greater in the bald than in the hairy site. However, although 5α-dihydrotestosterone formed about 20% of the total radioactivity, less than that due to unchanged testosterone, more than 10% was due to androstanedione. We may conclude, therefore, that a scalp remains hairy because it lacks 5α-reductase but that there

are no qualitative differences between the actual metabolites produced by hairy and bald areas.

The problem has, however, several other facets. First, it should not be assumed that 5α-dihydrotestosterone is necessarily the only active androgen in skin. When hair roots are incubated with labeled testosterone, androstenedione is the major metabolite [48,49]. In addition to 5α-dihydrotestosterone and androstenedione, androstanedione, androsterone, and androstanediols are formed in target organs. 5α-Androstane-3β,17β-diol, as well as androstenedione, significantly stimulates the sebaceous glands of hypophysectomized–castrated rats [50] even though such glands give only a very limited response to testosterone, possibly because of a failure of 5α-reduction. When tissues are incubated in vitro with [^{3}H]testosterone, the 3β, 17β-diol is a major metabolite of human scalp and back skin [51] and some women with idiopathic hirsutism or acne vulgaris excreted several times the normal amounts of androstanediol even though their levels of urinary testosterone were normal [52].

The possibility that more than one metabolite of testosterone is hormonally active is reinforced by the evidence that different androgenic steroids can affect target cells in different ways. Thus, in the seminal vesicles or preputial glands of the rat, both 5α-androstane-3β,17β-diol and 5α-androstane-3α, 17β-diol have similar effects on increases in DNA as 5α-dihydrotestosterone, but the 3α-diol has greater effect on cell metabolism [53]. In the sebaceous glands, too, cell division and intracellular lipid synthesis appear to respond differentially to different steroids [54].

A further point to consider is that the response of the target organ to androgens depends on the specific and selective attachment of the active steroid to receptor proteins in the cell. The process in the prostate, for example, is believed to involve the immediate binding of the steroid to a cytoplasmic receptor and its transfer, within 30 min, to the nucleus where it initiates new protein synthesis. A defect in the androgen receptor results in a failure of response; such a defect appears to explain the end-organ insensitivity to androgens in the hereditary disorder known as testicular feminization [55].

Specific cytosol receptors have been identified in the prostate [56] and the hamster sebaceous gland [57]. The possibility that 5α-androstanediols could be bound to a specific receptor in the cytoplasm and influence events at the translational as distinct from the transcriptional level has been considered by Robel et al [56]. These authors have established that 5α-androstane-3β,17β-diol, as well as 5α-dihydrotestosterone, is retained in a microsomal binding protein in rat ventral prostate, but they conclude that the physiologic significance of this is not yet established. The issue is, perhaps, confused by the demonstration that cytoplasmic extracts of canine prostate in vitro have a specific receptor protein for 5α-androstane-3α,17α-diol [58] and a claim that rat prostate cytosol will bind only 3α,17β-diol and not 3β,17β in vivo, and neither in vitro [59]. These authors concluded that the 3α,-17β-diol exerts its biologic effects mainly by conversion to 5α-dihydrotestosterone.

Though more needs to be done, abstruse discussion of exactly which active androgens are involved and where they are bound is premature. The solution to the problem of pattern baldness lies with the steroid molecules, the enzymes which convert them to active metabolites, and the proteins which bind them.

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